

Appl. No. 10/526,822  
Reply to Office Action of September 12, 2007

REMARKS/ARGUMENTS

The present invention as now claimed relates to a clear ophthalmic solution comprising latanoprost wherein turbidity due to a change of formulation is prevented by means of 1) using benzalkonium chloride represented by the formula of  $[C_6H_5CH_2N(CH_3)_2R]Cl$  (wherein R is alkyl having 12 carbon atoms) as the preservative, or by means of 2) adding essentially a nonionic tonicity agent only as a tonicity agent.

The claims are rejected over Dean et al, The Patent Abstract of Japan and further over Hellberg. However, as explained below, none of the references describe the ophthalmic solution of the present invention.

As described in the present specification, the inventors first confirmed the problem of white turbidity due to a change of formulation in ophthalmic solutions containing latanoprost at a certain concentration and benzalkonium chloride at a certain concentration, found means for preventing the white turbidity, i. e., means of 1) using benzalkonium chloride represented by the formula of  $[C_6H_5CH_2N(CH_3)_2R]Cl$  (wherein R is alkyl having 12 carbon atoms) as the preservative, and means of 2), adding essentially a nonionic tonicity agent only as a tonicity agent., and thereby solved the problem (See the present specification page 3, line 13 to page 4, line 7).

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None of the references describe or suggest at all the above-mentioned problem nor the means for solving the problem. Therefore, one of ordinary skill in the art is not lead to the present invention from any of the references that do not describe the problem or the means for solving the problem.

**Dean et al. (U.S. Patent 6,166,073)** merely describe compositions containing DP-agonist and FP-agonist prostaglandin agonists for treating glaucoma or ocular hypertension. Dean et al. do not describe or suggest at all the problem of white turbidity due to a change of formulation in ophthalmic solutions containing latanoprost and benzalkonium chloride. Further, Dean et al. do not describe or suggest all the means for preventing white turbidity.

**The Patent Abstract of Japan** merely describes a method of producing tonicity aqueous solution, comprising using polyhydric alcohol as a tonicity agent. There is no description or suggestion at all in the Patent Abstract of Japan either change of formulation or about latanoprost.

**Hellberg et al. (U.S. Patent 6,646,001)** merely describe compositions for the treatment of glaucoma and ocular hypertension, comprising a prostaglandin FP. receptor agonist and a prostaglandin synthesis inhibitor. Hellberg et al. do not describe or

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suggest at all the problem of white turbidity due to a change of formulation in ophthalmic solutions containing latanoprost and benzalkonium chloride. Further, Hellberg et al. do not describe or suggest at all the means for preventing white turbidity.

As discussed above, none of the references describe or suggest at all the problem that white turbidity is observed due to a change of formulation in ophthalmic solutions containing latanoprost at a certain concentration and benzalkonium chloride at a certain concentration nor any analogous problem.

The present invention uses either of the means of 1), using benzalkonium chloride represented by the formula: of  $[C_6H_5CH_2N(CH_3)_2R]Cl$  (wherein R is alkyl having 12 carbon atoms) as the preservative, or 2) adding essentially a nonionic tonicity agent only as a tonicity agent; in order to prevent white turbidity due to a change of formulation.

In means 1), benzalkonium chloride having 12 carbon atoms is used.

Since none of the references describe the problem of white turbidity nor benzalkonium chloride having 12 carbon atoms, nor a related problem, there is no reason to look to these references for a solution. Even if you do look, the use of benzalkonium chloride having 12 carbon atoms is not obvious as a means for solving the problem. Since, the present invention

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according to means 1) exhibits a novel effect of preventing white turbidity, which is not a problem to be solved in the references but in the present invention, such an effect can not be obvious from the references where even the problem of white turbidity is not described. Hence, the ophthalmic solution formulated according to means 1) of the present invention exhibits a novel effect, or an unexpected effect, and thereby meets the unobviousness requirement.

In means 2), a nonionic tonicity agent alone is essentially added as a tonicity agent whereby white turbidity due to a change of formulation is prevented: This means is introduced following the inventor's focus on the fact that the use of the salts as a tonicity agent is a cause of white turbidity. This is not suggested in the art and it is impossible to lead to the ophthalmic solution wherein a nonionic tonicity agent alone is essentially added as a tonicity agent, as a means for solving the problem from the art. Moreover, as with the present invention according to means 1), the present invention according to means 2) also exhibits a novel effect of preventing white turbidity, which is not a problem to be solved in the references but in the present invention, and therefore, such an effect can not be obvious from the references where even the problem of white turbidity is not described. Hence, the ophthalmic solution formulated according to means 2) of, the present invention

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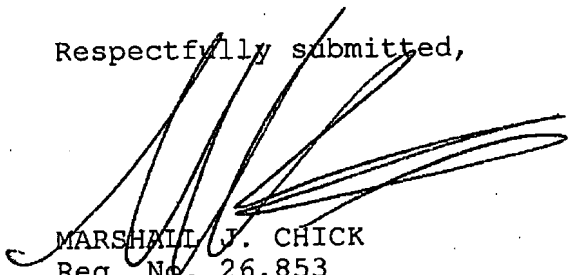
exhibits a novel effect, or an unexpected effect; and thereby meets the unobviousness requirement.

As discussed above, the present invention is not shown or suggested from the references taken alone or in any combination where there is no description or suggestion of the problem to be solved by the present invention, exhibits a novel and unexpected effect, and therefore satisfies the unobviousness requirement.

In view of the above, the rejections are avoided. Allowance of the application is therefore respectfully requested.

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Respectfully submitted,



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Encs.: Request for Continued Examination (RCE)  
PTO-2038 for \$810  
Petition for Extension of Time - two month  
PTO-2038 for \$460